

## Diagnosis of Ovarian Cancer

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# CLINICAL REVIEW

## Diagnosis of ovarian cancer

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Ovarian cancer is the seventh most common cancer in women worldwide, with 239 000 new cases diagnosed in 2012.<sup>1</sup> As with many other types of cancer, geographical variation in the incidence of and mortality from ovarian cancer is substantial, with a higher incidence in economically developed regions of the world.<sup>2</sup> Incidence is highest in the 50-70 year old age group, with 75% of cases diagnosed in women aged more than 55 years.<sup>3</sup> In 80% of women the disease will be advanced at presentation, with a low five year survival rate; the all stage five year survival in the United Kingdom is 46%.<sup>4</sup> This low survival rate in the UK has been recognised in the International Cancer Benchmarking Partnership and has been attributed at least partly to less timely diagnosis.<sup>5</sup> This review summarises the presenting features, diagnostic tests, risk factors, and groups at high risk of ovarian cancer and is aimed at primary care practitioners and hospital doctors in other specialties.

### What are the types of ovarian cancer and why is this relevant?

Ovarian cancer refers to a diverse set of histological types of cancers. Most ovarian cancers are epithelial in origin, with high grade serous carcinomas accounting for 70-80% of cases and the rarer types, including clear cell (3%), endometrioid (<5%), and mucinous (<3%) cancer.<sup>6</sup> Non-epithelial histology types include the rarer germ cell tumours and stromal tumours.

Differences in histology correlate with differences in molecular characteristics and clinical behaviour. Currently, on the basis of clinical or molecular and histological patterns, ovarian cancer can be divided into two types—type 1, which comprises clear cell, mucinous, endometrioid, and low grade serous cancer histology, and type 2, which comprises high grade serous cancers. Type 1 cancers tend to be slow growing, indolent, and more likely to be detected earlier by ultrasonography, whereas type 2 cancers are typically fast growing and spread early. Paradoxically, type 1 cancers can be more challenging to treat, as these tumour types are less chemosensitive.

One important development in recent years is the recognition that the primary source of previously termed “ovarian” cancer is in fact the distal end of the fallopian tube, and seemingly the

main site of origin for many high grade serous cancers. This has implications for both screening and preventive strategies.<sup>7</sup>

### What risk factors are associated with ovarian cancer?

#### Epidemiological risk factors

Epidemiological studies show that the number of ovulatory cycles a woman has in her lifetime is proportional to her risk of developing ovarian cancer, with reduced numbers of ovulatory cycles such as from pregnancy or the use of the contraceptive pill being associated with a protective effect. Conversely, nulliparity, a history of breast cancer, and a familial history of breast and ovarian cancer are recognised risk factors, with recent reports suggesting a small increased risk with hormone replacement therapy.<sup>8</sup> Ovarian cancer is also much more common in the postmenopausal age group.<sup>3</sup>

#### Genetic risk factors

Large cohort studies show that in approximately 20% of women an inherited genetic mutation confers a higher risk of developing ovarian cancer.<sup>9</sup> By age 70 the lifetime risk of ovarian cancer and breast cancer in women with a BRCA1 mutation is as much as 63% and 85%, respectively, and in women with a BRCA2 mutation it is as much as 27% and 84%, respectively.<sup>10</sup> Therefore women with a strong family history of breast and ovarian cancer or a known history of a BRCA mutation should be considered at higher risk of ovarian cancer.

The Jewish community, particularly the Ashkenazi population, has a high rate of BRCA mutations and should be considered at increased risk for the development of both breast and ovarian cancer. Two large prospective studies testing Jewish communities in Israel and London, irrespective of family history, for three founder mutations in the BRCA genes showed that one in three women with BRCA mutations did not have a family history of cancer.<sup>11 12</sup> Large case-control series showed that women with BRCA mutations tend to have tumours that are sensitive to platinum and have visceral metastases, with 10 year survival that is similar to cohorts without the BRCA mutations.

**The bottom line**

- NICE recommends symptom triggered testing using sequential CA125 and ultrasonography for ovarian cancer
- Ovarian cancer is most common in the postmenopausal age group
- CA125 is not a specific marker in premenopausal women and may be increased during menstruation and in other conditions
- Ovarian cysts are common in premenopausal women and may be physiological
- Ultrasound findings of simple or unilocular cysts (that is, fluid-containing cysts) measuring <5 cm on ultrasonography are reassuring and associated with less than a 1% risk of malignancy
- All women with a diagnosis of high grade serous ovarian cancer may be offered routine testing for BRCA. Women with known BRCA mutations may be offered risk reducing surgery to remove the fallopian tubes and ovaries

**Sources and selection criteria**

We carried out an electronic search of PubMed, Medline, Embase, the Cochrane Library, and the Cochrane database of systematic reviews using the search term "ovarian cancer." Only those papers that were written in English, were published within the past 10 years, and described studies with adequate scientific validity were considered. We also referred to personal archives of papers from 2009 to 2015 and guidance documents from the National Institute for Health and Care Excellence (CG122 and NG12). A comprehensive evidence review was performed during 2009-10 by the National Collaborating Centre for Cancer, on which NICE clinical guidance CG122 is based.

Combined 10 year overall survival rates were 30% for non-carriers of BRCA mutations, 25% for BRCA1 carriers, and 35% (95% confidence interval 30% to 41%) for BRCA2 carriers.<sup>13</sup>

## How do women with ovarian cancer present?

Recent retrospective case-control studies found that women generally have several persistent or frequently occurring non-specific symptoms including abdominal distension or "bloating," a feeling of fullness or loss of appetite, pelvic or abdominal pain, increased urinary urgency or frequency, unexplained weight loss, fatigue, or changes in bowel habit.<sup>14 15</sup> These symptoms are common; interrogation of general practice databases suggests that on average one in two women between the ages of 45 and 70 consult their general practitioner each year with these symptoms.<sup>16-18</sup> This presents a diagnostic dilemma for doctors, given the low incidence of ovarian cancer (an average UK general practitioner sees one woman with ovarian cancer once every 3-5 years), the low positive predictive value of symptoms,<sup>15 19</sup> and the lack of clear diagnostic pathways. A large survey of UK patients' experiences found that 36% of women with a subsequent diagnosis of ovarian cancer, present to their general practitioner with symptoms three or more times before diagnosis.<sup>20</sup> In the UK the mean time from first symptoms to first presentation is 39 days and the mean time from first presentation to diagnosis is 21 days.<sup>21</sup> Indeed, ovarian cancer is one of several cancers classified as "harder to suspect."<sup>22</sup> Analysis of routes to diagnosis in routinely collected national datasets shows that almost one third of women with ovarian cancer in the UK receive a diagnosis through emergency departments and a further third through cross specialty referrals.<sup>23</sup> Women presenting at emergency departments often have ascites, pleural effusions, bowel obstruction, and low albumin levels impacting adversely on treatment choices and survival. Women presenting as emergencies have a worse survival than those diagnosed electively through rapid access clinics.<sup>23 24</sup>

## When should ovarian cancer be suspected in primary care?

Guidance from the National Institute for Health and Care Excellence in the UK and the US based National Comprehensive Cancer Network recommend symptom triggered testing for

ovarian cancer.<sup>25 26</sup> Women with persistent symptoms of abdominal distension or "bloating," early satiety, loss of appetite, pelvic or abdominal pain, increased urinary urgency or frequency, unexplained weight loss, fatigue, or changes in bowel habit should be tested in the primary care setting and referred urgently to secondary care, with the aim of achieving faster diagnosis and treatment, and thereby improved survival. NICE recommends sequential testing of serum CA125 followed by abdominopelvic ultrasonography if the serum CA125 level is 35 IU/L or more. Women with clinical findings of ascites and a pelvic or abdominal mass should be referred urgently (figure 1).

These recommendations were based on evidence from case-control studies, but since then two large well conducted prospective studies with over 6500 women have been published showing that symptom triggered diagnostic testing of CA125 level and ultrasonography for ovarian cancer does not result in a stage shift in ovarian cancer but may result in more patients undergoing complete removal of tumour at surgery suggesting lesser tumour load in women detected through symptom triggered testing.<sup>27 28</sup> At present the impact on mortality with a strategy of symptom triggered diagnostic testing is not known.

The implementation of symptom triggered testing is challenging in clinical practice. A survey of general practitioners found that most would refer patients on the basis of increased CA125 levels even if the ultrasonography finding was normal.<sup>29</sup> A recent audit of outcomes in two week wait clinics in pre-guideline and post-guideline cohorts showed that current implementation has led to an increase in the predictive value of detecting cancer through rapid access clinics but no impact on stage at presentation.<sup>30</sup> This audit also reported that for most referrals guidance for sequential testing for suspected ovarian cancer was not followed (90%), most had heterogeneous symptoms, and most were made on the basis of what the doctor considered either increased CA125 levels or abnormal ultrasonography findings. Furthermore, most women referred (66%) were premenopausal, where the risk of ovarian cancer is low.<sup>30</sup> NICE did not issue any age limits in guidance; however, it was emphasised that the high risk group was women aged more than 50 years.

## Are CA125 tests and ultrasonography reliable?

### CA125 testing

CA125 is a non-specific marker, the levels of which can be increased in several conditions, many associated with benign

conditions—for example, endometriosis and menstruation. This needs to be remembered when women are counselled (see box), as should the fact that the development of an ovarian cyst is a physiological prerequisite to ovulation. A further complicating factor is that the level of CA125 is only increased in 50% of stage 1 cancers.

## Ultrasonography

Currently there is no universally agreed scoring system to triage women with suspected benign or malignant adnexal masses detected by ultrasonography at primary care level. This can create a difficulty for general practitioners in interpreting reports from the US, particularly as NICE guidance does not contain recommendations on what constitutes abnormal ultrasonography findings. Ovarian masses that are multilocular, bilateral, solid, or associated with ascites and metastasis are extremely suspicious and should prompt rapid referral. Data from the UK Collaborative Trial of Ovarian Cancer Screening in primary care and other large prospective studies in secondary care show that findings of simple or unilocular cysts (that is, fluid-containing cysts), measuring <5 cm on ultrasonography are reassuring and associated with a less than 1% risk of malignancy.<sup>31 32</sup> Large prospective studies from the International Ovarian Tumour Analysis consortium suggest that utilising “m” (malignant) and “b” (benign) rules to identify masses as suspicious may be highly accurate. Using these rules, the reported sensitivity was 95%, specificity 91%, positive likelihood ratio 10.37, and negative likelihood ratio 0.06.<sup>33</sup> The accuracy of these rules has been demonstrated in secondary care, predominantly with specialists in ultrasonography. Translating this to a primary care setting may have a positive impact but is possibly challenging to achieve owing to variation in ultrasound services and providers and in achieving quality assurance.

## How can ovarian cancer be detected in premenopausal women?

One important group of women should be highlighted, although their situation is rare. Germ cell tumours must be suspected in women aged less than 25 with a pelvic mass and these women should be referred urgently to hospital as conservative surgery followed by chemotherapy can be lifesaving. Increased levels of tumour markers  $\beta$  human chorionic gonadotrophin, alpha fetoprotein, and lactate dehydrogenase can aid diagnosis in this subset and should be requested but should not delay referral.

By the age of 65 years, 4% of women will have been admitted to hospital with an ovarian cyst, making this the fourth most common gynaecological reason for hospital admission in England.<sup>4</sup> In the UK each year about 1000 women aged less than 50 will receive a diagnosis of ovarian cancer. Among premenopausal women, more than 90% of surgically managed cases are benign, compared with just 60% in the postmenopausal population.

The present recommendation for referral by a general practitioner is based on symptoms and the results of the CA125 test, although optimal diagnostic pathways for premenopausal women with a complex ovarian mass and increased CA125 levels are not defined. Greatly increased levels of CA125 (>200 units/mL) or rapidly increasing levels should be considered more suspicious in this group.<sup>34</sup> Women may be reassured to know that the CA125 test can be abnormal as a result of menstruation, and that ovarian cysts can be physiological.

Research focusing on women who are referred with symptoms and increased CA125 levels or abnormal adnexal masses, aims to enhance the ability to triage women appropriately. The ROCKETS project ([www.birmingham.ac.uk/ROCKETS](http://www.birmingham.ac.uk/ROCKETS)) has been funded by the National Institute for Health Research to identify, derive, and validate improved tests and risk scores for premenopausal and postmenopausal women in both primary and secondary care. This project is under way and should provide useful information on optimal diagnostic pathways in the future.

## What is the role of screening and prevention strategies?

One large randomised US based trial compared annual screening using CA125 testing and ultrasonography, with volunteers in the control arm not undergoing any investigations. This trial did not find a stage shift or mortality benefit from this screening strategy in ovarian cancer. However, the largest randomised controlled trial, the UK Collaborative Trial of Ovarian Cancer Screening (200 000 women), which evaluates a different screening strategy using a ROCA (risk of ovarian cancer algorithm) constructed on serial CA125 levels is due to report later this year, and the results are awaited with interest. The most recent results from the trial show that serial testing with the ROCA algorithm doubles the number of ovarian cancers detected compared with testing using single thresholds of CA125.<sup>35</sup>

Given the recent understanding that the fimbrial end of the fallopian tube is the starting site of neoplastic transformation for many women, population based opportunistic postpartum salpingectomy is now being evaluated in British Columbia, Canada, as a prevention strategy for epithelial ovarian cancer.<sup>36</sup> Long term incidence and mortality data are expected in 10 years.

## What is recommended for women with a known genetic predisposition?

Risk reducing salpingo-oophorectomy has been widely adopted as a key component of breast and gynaecological cancer risk reduction for women with BRCA1 and BRCA2 mutations once they have completed their families.<sup>37</sup> Alternative strategies such as delayed salpingectomy to spare the menopause have been proposed. The large UK Familial Ovarian Cancer Screening study in BRCA mutation carriers shows that surveillance with four monthly CA125 testing and ultrasonography does not reduce mortality from ovarian cancer.<sup>38</sup>

## Are there any tests on the horizon?

Better “tests” to discriminate between malignant and benign ovarian masses would be most welcome, as this would reduce unnecessary testing, hospital visits, and, importantly, the distress associated with a diagnosis of possible malignancy when that may not be the case. Newer biomarkers such as HE4 or OVA1 both singly or in conjunction with CA125 may improve the detection of ovarian cancer; neither has been tested in the primary care population yet. Novel testing using sophisticated genomic technology shows considerable promise in the early detection of ovarian cancer. Plasma circulating tumour DNA can identify small tumour loads. A recent study in a small series of 40 women showed that it was possible to identify accurately cells shed by ovarian tumours into cervical smears.<sup>39 40</sup> Both tests are worthy of future investigation.



**What to tell women undergoing a CA125 test**

- This blood test measures a protein called CA125 in your blood
- The level of CA125 can be increased in several conditions, including endometriosis, menstruation, ovarian cysts, diverticulitis, and sometimes ovarian cancer. So having increased levels of CA125 does not necessarily mean you have ovarian cancer
- If the result shows an increased level, then your doctor will arrange an ultrasound scan of your ovaries
- If the test comes back at a very increased level your doctor will refer you to see a specialist
- A normal level does not rule out ovarian cancer (especially at an early stage), so if your symptoms persist then you will need to see your doctor again. Keeping a symptoms diary may be helpful before a further consultation

**What treatments are available for ovarian cancer?**

The mainstay of treating ovarian cancer is a combination of surgery and chemotherapy—the latter normally platinum based. The best outcomes are in women with early stage disease, and in those with advanced disease, where the entire tumour is surgically removed and the disease is sensitive to platinum based chemotherapy. Even in the most favourable group treated for advanced disease, about 70% will relapse within 18 months.<sup>41</sup> In some women with advanced disease, initial chemotherapy rather than surgery may be deemed the better approach, with surgery delayed until after three chemotherapy cycles.<sup>42</sup>

Depending on the timing of relapse of disease, some women will achieve long remissions, but the reality is that management at relapse is palliative rather than curative. Treatment at this stage will be mainly chemotherapy (or other agents), and indeed surgery may have a role in selected women.

**What are the survival statistics?**

Ten year survival remains poor, at 35%. Survival from ovarian cancer is highly stage dependent (five year relative survival 92% stage I v 5% stage IV).<sup>43</sup> A shift at stage of presentation or a reduction in tumour load at stages III/IV ovarian cancer is likely to substantially improve survival from ovarian cancer and must be essential aims of future research and change implementation programmes in the National Health Service.

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### A patient's perspective

I researched my family tree and highlighted every member who has had cancer. It is covered in yellow highlighter pen.

My maternal grandmother died aged just 34. Three of her four children had cancer. I have four cousins under 50 who have had cancer. My poor family has been devastated by cancer.

In 2007 I had a mammography which detected breast cancer. I had no symptoms, but told the cancer specialists about my cousins. They said they were not closely related and not to worry. I had a lumpectomy, four lymph glands removed, radiotherapy, and tamoxifen. I took four days off work.

Three years later one of my cousins died of breast cancer and my general practitioner agreed to a genetic test. I was BRCA2 positive, which explained my sad family history. I was counselled and once I knew the risks of ovarian cancer I decided to have my ovaries removed. My daughter was tested and was negative, thank goodness.

My ovaries were removed in 2012. No follow-up was required and I thought I had sorted it. But I started feeling bloated and I had indigestion and felt tired. I dismissed this as overeating and part of the healing process and my GP agreed. My symptoms worsened and I had a blood test—which showed my CA125 level to be 3800. My GP then discovered that the histology reports from my ovarian surgery were still outstanding.

Once recovered, they revealed that at the time of my surgery my tissue had tested positive for grade 1c ovarian cancer. This information had been lost in the system. By now I had stage 3c high grade serous adenocarcinoma of the fallopian tubes.

I just sat there, completely unable to take in the seriousness of my situation. I left to go home—I live on my own—and looked up ovarian cancer through Google, which was a bad move.

A scan revealed the cancer had spread to my sternum, pulmonary tissue, and peritoneum. I was told I did not have long to live. I started chemotherapy and my oncologist said I had a 20% survival rate and an 80% chance of recurrence, with two to three years to live.

Somehow I have come through this.

Telling the medical students about my experience and answering their questions means my story can teach them about diagnosis and communication and about seeing women like me in the context of our families and our whole lives. They really listened hard.

The students wanted to know if I was angry, but I'm not, not now. They asked me how bad news should be delivered and I said not when you're alone like I was. The students also wanted to know more about ongoing side effects from chemotherapy, so we had a good chat about that.

This project has given me confidence to speak about my cancer, which is very personal and was a terrible trauma. The students really wanted to hear me.

To know more about "Survivors teaching students", please contact the charity Ovacome on [RuthG@ovacome.org.uk](mailto:RuthG@ovacome.org.uk) or [www.ovacome.org.uk/](http://www.ovacome.org.uk/)

### Questions for future research

What are optimal pathways of diagnosis in primary and secondary care in premenopausal and postmenopausal women with non-specific symptoms ([www.birmingham.ac.uk/ROCKETS](http://www.birmingham.ac.uk/ROCKETS))?

Can novel technologies (for example, plasma circulating tumour DNA, sequencing of exfoliated tumour DNA in cervical smears, urine steroid profiles) improve diagnostic testing for ovarian cancer?

What are best surveillance strategies in patients with BRCA mutations who are at high risk for the development of ovarian cancer?

Can multidisciplinary clinics investigating women with non-specific symptoms improve earlier detection of ovarian cancer?

Can general practitioners identify patients for investigation or refer differently to improve earlier detection of ovarian cancer?

### Additional educational resources

#### Resources for healthcare professionals

##### Target Ovarian Cancer websites

[www.targetovariancancer.org.uk/health-professionals/gps/diagnosing-ovarian-cancer](http://www.targetovariancancer.org.uk/health-professionals/gps/diagnosing-ovarian-cancer)—advice for general practitioners about diagnosing ovarian cancer

[www.targetovariancancer.org.uk/health-professionals/gps/get-trained](http://www.targetovariancancer.org.uk/health-professionals/gps/get-trained)—free online learning tools for general practitioners to help them diagnose ovarian cancer

##### Resources for patients

[www.targetovariancancer.org.uk](http://www.targetovariancancer.org.uk), [www.ovacome.org.uk](http://www.ovacome.org.uk), and [www.ovarian.org.uk](http://www.ovarian.org.uk)—websites providing women with an up to date guide on the management options after a diagnosis of ovarian cancer

[www.targetovariancancer.org.uk/about-ovarian-cancer/what-ovarian-cancer/ovarian-cancer-symptoms](http://www.targetovariancancer.org.uk/about-ovarian-cancer/what-ovarian-cancer/ovarian-cancer-symptoms)—describes the symptoms of ovarian cancer and includes a video

[www.targetovariancancer.org.uk/sites/default/files/Target-Ovarian-Cancer-symptoms-leaflet.pdf](http://www.targetovariancancer.org.uk/sites/default/files/Target-Ovarian-Cancer-symptoms-leaflet.pdf)—downloadable leaflet (PDF) discussing symptoms

[www.targetovariancancer.org.uk/about-ovarian-cancer/familial-ovarian-cancer/symptoms-and-risks-factors](http://www.targetovariancancer.org.uk/about-ovarian-cancer/familial-ovarian-cancer/symptoms-and-risks-factors)—discusses familial risk and includes a link to Macmillan's online risk assessment tool (OPERA)

[www.targetovariancancer.org.uk/sites/default/files/Ovarian%20cancer%20information/10-top-tips-for-patients-seeing-GPs-about-ovarian-cancer\\_0.pdf](http://www.targetovariancancer.org.uk/sites/default/files/Ovarian%20cancer%20information/10-top-tips-for-patients-seeing-GPs-about-ovarian-cancer_0.pdf)—downloadable leaflet (PDF) with top 10 tips for seeing your general practitioner

[www.targetovariancancer.org.uk/sites/default/files/Ovarian%20cancer%20information/CA125-factsheet-for-ovarian-cancer-tests-Target-Ovarian-Cancer-2015.pdf](http://www.targetovariancancer.org.uk/sites/default/files/Ovarian%20cancer%20information/CA125-factsheet-for-ovarian-cancer-tests-Target-Ovarian-Cancer-2015.pdf)—downloadable leaflet (PDF) on CA125

[www.targetovariancancer.org.uk/sites/default/files/Ovarian%20cancer%20information/Ultrasound-factsheet-for-ovarian-cancer-tests-Target-Ovarian-Cancer-2015\\_0.pdf](http://www.targetovariancancer.org.uk/sites/default/files/Ovarian%20cancer%20information/Ultrasound-factsheet-for-ovarian-cancer-tests-Target-Ovarian-Cancer-2015_0.pdf)—downloadable leaflet (PDF) on ultrasonography for suspected ovarian cancer

### How were patients included in the creation of this article?

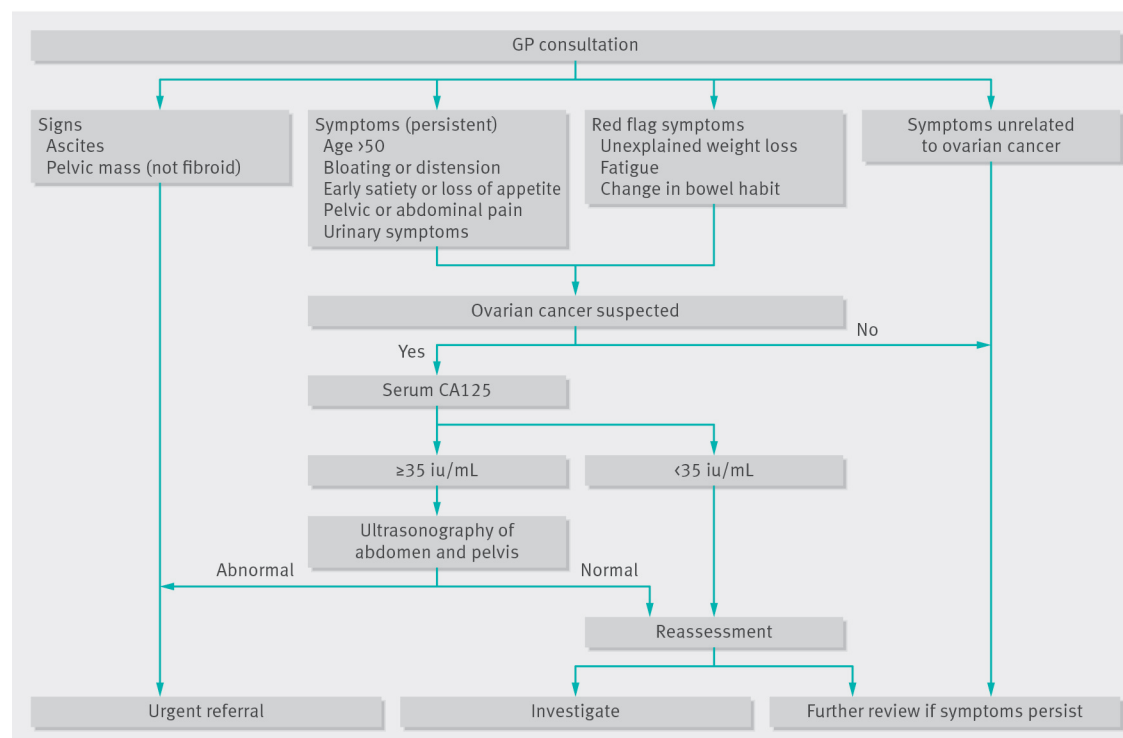
A patient who talked to medical students in October 2014 about her experience as part of "Survivors teaching students" has given an account of her experience in the patient perspective box.

- 42 Kehoe S, Hook J, Nankivell M, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. *Lancet* 2015;386:249-57.
- 43 Cancer Research UK. 2013. [www.cancerresearchuk.org/cancer-info/cancerstats/types/ovary/survival/ovarian-cancer-survival-statistics](http://www.cancerresearchuk.org/cancer-info/cancerstats/types/ovary/survival/ovarian-cancer-survival-statistics).

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## Figure



Flow chart for diagnosis of ovarian cancer. Adapted from NICE<sup>26</sup>